General

Guideline Title

American Gastroenterological Association Institute guideline on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions.

Bibliographic Source(s)

Yang YX, Brill J, Krishnan P, Leontiadis G, Clinical Guidelines Committee. American Gastroenterological Association Institute guideline onÂ the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology. 2015 Oct;149(4):1082-7. [7 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of evidence (high, moderate, low, very low) and strength of recommendation (strong, weak) are provided at the end of the "Major Recommendations" field.

Esophagus

1. In patients undergoing esophagogastroduodenoscopy (EGD) for dyspepsia as the sole indication, the American Gastroenterological Association (AGA) recommends against obtaining routine biopsies of the normal-appearing esophagus or gastroesophageal (GE) junction regardless of immune status. (Strong recommendation, Very low quality evidence)

Stomach

2. In immunocompetent patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends obtaining routine biopsies of the normal-appearing gastric body and antrum for the detection of *Helicobacter pylori* (HP) infection if the HP infection status is unknown. (Strong recommendation, Moderate quality evidence)
3. In immunocompromised patients undergoing EGD for dyspepsia as the sole indication, the AGA recommends obtaining routine biopsies of the normal-appearing gastric body and antrum for the detection of HP infection if the HP infection status is unknown. (Strong recommendation, Very low quality evidence)
4. When obtaining biopsies from the normal-appearing gastric body and antrum for the detection of HP infection, the AGA suggests following the 5-biopsy Sydney System, with all specimens placed in the same jar. (Conditional recommendation; Moderate quality evidence)

5. When biopsies are obtained from the normal-appearing gastric body and antrum for the detection of HP infection, the AGA suggests not obtaining automatic special staining of the specimens. (Conditional recommendation; Moderate quality evidence)

Duodenum

6. In patients undergoing EGD for dyspepsia as the sole indication, and in the absence of other signs or symptoms associated with an increased risk of celiac disease, the AGA suggests not obtaining routine biopsies of the normal-appearing duodenum to detect celiac disease. (Conditional recommendation; Very low quality evidence)
7. In immunocompromised patients undergoing EGD for dyspepsia as the sole indication, the AGA suggests obtaining routine biopsies of the normal-appearing duodenum for the detection of graft-vs-host disease (GVHD) in postallogeneic tissue transplantation patients and for opportunistic infections. (Conditional recommendation; Very low quality evidence)
8. When biopsies are obtained from the normal-appearing duodenum, the AGA suggests not performing routine special staining of the specimens. (Conditional recommendation; Very low quality evidence)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions on Quality of Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect might be substantially different from the estimate of the effect.
Very Low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE Definitions on Strength of Recommendation

	For the Patient	**For the Clinician**
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Weak/Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids might well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Clinical Algorithm(s)

An algorithm titled "American Gastroenterological Association Institute Guideline on the Role of Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Adult Patient in the Absence of Visible Mucosal Lesions: Clinical Decision Support Tool" is provided (see the "Availability of Companion Documents" field).

Scope

Disease/Condition(s)

Dyspepsia

Note: Dyspepsia is defined according to the Rome III criteria, which include 1 or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain, and epigastric burning. In addition, this guideline assumes no prior treatment for *Helicobacter pylori* (HP) infection.

Guideline Category

Evaluation

Clinical Specialty

Gastroenterology

Intended Users

Physicians

Guideline Objective(s)

To establish evidence-based practicing standards for the performance of biopsies of normal-appearing mucosa in the upper gastrointestinal tract

Target Population

Adult patients (i.e., older than 18 years of age) who are undergoing esophagogastroduodenoscopy (EGD) with dyspepsia as the sole indication

Interventions and Practices Considered

1. Routine biopsies for immunocompetent and immunocompromised patients undergoing esophagogastroduodenoscopy (EGD)
    - Gastric body and antrum for the detection of *Helicobacter pylori* (HP) infection
    - Duodenum for the detection of graft-vs-host disease (GVHD) in postallogeneic tissue transplantation patients and for opportunistic infections
2. Routine biopsies of the normal-appearing esophagus or gastroesophageal (GE) junction (not recommended)
3. 5-Biopsy Sidney System for obtaining biopsies
    - All specimens placed in same jar
    - No special staining of specimens

Major Outcomes Considered

- Resolution or improvement of dyspeptic symptoms
- Changes in quality of life
- Effect on survival/mortality after treating the disorder (histologic reflux esophagitis) that was diagnosed by biopsying normal-looking mucosa
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Information Sources and Study Selection

A Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist, with input from the technical review authors and a medical librarian, developed and conducted several serial literature searches. The following bibliographic databases were searched through the OVID interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) on November 18, 2013. The main search strategy consisted of controlled vocabulary, including the National Library of Medicine's Medical Subject Headings (MeSH) that were exploded, as well as free text words. The main terms included and combined were terms related to "biopsy," "histology," "microscopy," "immunohistochemistry," or "staining" combined with terms related to "dyspepsia." The exact synthesis of the main search strategy is provided in Appendix 1 of the technical review (see the "Availability of Companion Documents" field).

The results were limited to English language and humans. The technical review authors applied filters to exclude conference abstracts, editorials, letters to the editor, and case reports. No limitations were applied on the year of publication. The criterion for selecting studies was compatibility with the patient population, intervention, comparator, and outcome (PICO) frame as defined in the technical review. Each title and abstract of the references identified by the search was independently checked by at least 2 authors, who removed obviously irrelevant reports. The full text of all potentially relevant studies was obtained and assessed for relevance to this project, again by at least 2 authors. The final decisions on inclusion were based on consensus. The technical review authors included primary studies and systematic reviews. In selecting studies, they followed the umbrella systematic review approach in which they identified published systematic reviews that fit predetermined eligibility criteria and ranked articles based on publication type and methodological rigor.

A systematic review was eligible for inclusion if it evaluated the outcomes of interest mentioned (i.e., outcomes important to patients). The technical review authors supplemented this by trying to identify any additional randomized controlled trials (RCTs) not included in the systematic reviews, as well as references of relevant articles from the systematic reviews. When the systematic reviews did not provide sufficient information to fully apply the GRADE approach (such as rigorous assessment of risk of bias, assessment of heterogeneity, and adequate description of studies to judge directness), they attempted to retrieve and assess the individual primary studies. When systematic reviews were not up to date or were incomplete, the technical review authors performed additional focused literature searches in MEDLINE and attempted to perform their own systematic reviews and meta-analyses using the Cochrane Collaboration's RevMan (Review Manager, 2014, version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Number of Source Documents

The guideline developers retrieved 2041 records from the literature search. After review, 321 publications were eventually included. The characteristics of the studies are shown in Table 1 to Table 10 in the technical review (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions on Quality of Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect might be substantially different from the estimate of the effect.
Very Low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

When systematic reviews were not up to date or were incomplete, the technical review authors performed additional focused literature searches in MEDLINE and attempted to perform their own systematic reviews and meta-analyses using the Cochrane Collaboration's RevMan (Review Manager, 2014, version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Evaluating the Evidence: Risk of Bias and Study Quality Appraisal

Within the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, randomized controlled trials (RCTs) start as high-quality evidence but can be rated down for 5 possible reasons. Using GRADE, the quality of evidence for each outcome was evaluated for the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. When the systematic reviews did not provide sufficient information to judge the quality of the evidence, individual studies were retrieved. Evidence ratings and qualitative judgments were determined via video conference discussion and consensus. For each question, an overall judgment of quality of evidence was made for a body of evidence that encompassed all critical outcomes.

When available, quantitative estimates of effect were applied from existing systematic reviews. Quality of evidence was presented in the form of answers to the 2 major questions for each anatomic region as discussed. Answers to the question are organized around major conditions of interest for each organ.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline was developed by the American Gastroenterological Association's (AGA) Clinical Practice Guidelines Committee and approved by the AGA Governing Board.

This guideline was developed utilizing the AGA Process for Developing Guidelines (see the "Availability of Companion Documents"). Briefly, the AGA process for developing clinical practice guidelines incorporates the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and best practices for generating trustworthy guidelines as outlined by the Institute of Medicine. GRADE methodology was utilized to prepare the background information for the guideline and the technical review that accompanies it. Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review, authored by a multidisciplinary panel that included a gastrointestinal pathologist. In preparation for the formulation of the current guideline recommendations, the guideline panel and the authors of the technical review met face to face in January 2015 to systematically review the quality, quantity, and consistency of the available aggregate evidence and consider other factors relevant for the risk-to-benefit assessment of the eventual recommendations. Although critically important, it must be underscored that evidence quality was not the only factor considered in the formulation of the recommendations. Other considerations, wherever appropriate, included comparison of the benefits and harms of particular recommendation, economic value, and potential variations in patient preference. In addition, these guidelines are developed based primarily on evidence derived from Western populations. Certain non-Western populations might have sufficiently high risk for upper gastrointestinal abnormalities to warrant a risk-tailored management approach. Finally, the endoscopic biopsy itself was assumed to be associated with a negligible rate of complications.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions on Strength of Recommendation

	For the Patient	For the Clinician

	For the Patient	For the Clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Weak/Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids might well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the absence of mucosal lesions. The guideline was developed by the AGA's Clinical Practice Guidelines Committee and approved by the AGA Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Despite the overall low quality of the evidence, there are substantial data, including those from randomized controlled trials (RCTs), supporting a clinically important benefit to detecting and eradicating *Helicobacter pylori* (HP) infection in patients with dyspepsia, both with respect to symptomatic relief and gastric cancer risk reduction. A strong recommendation for obtaining routine biopsies for the detection of HP in patients with dyspepsia was justified. Notably, in patients whose HP infection status is already known, this recommendation would not apply, as the assumed benefit would not be present.
- A strong recommendation against obtaining routine biopsy of normal-appearing esophagus and gastroesophageal (GE) junction was believed to be justified, despite the very-low-quality evidence. Nevertheless, in certain populations (e.g., Iranian and Chinese) at high risk for squamous dysplasia, which could be associated with subtle mucosal changes, risk-tailored management considerations might be warranted.

Potential Harms

One must consider the potential for false-positive biopsy diagnosis in celiac disease among patients with dyspepsia, particularly when only early-grade celiac changes (e.g., Marsh I-II) are detected. Because this recommendation is primarily dependent on very-low-quality prevalence data, a conditional recommendation is warranted. As the possibility exists that the true prevalence of celiac disease among patients presenting with dyspepsia might be higher than what the current literature suggests, the recommendation against obtaining routine biopsies of the normal-appearing

duodenum to detect celiac disease might need to be updated when higher-quality evidence becomes available. Biopsy of the normal-appearing duodenum might be appropriate in patients who are at high risk for celiac disease, as specified by a previous American Gastroenterological Association (AGA) guideline on the diagnosis and management of celiac disease.

Qualifying Statements

Qualifying Statements

These standards are intended to reduce practice variation and promote high-value care. It is important to recognize that there are areas of scientific uncertainty due to low-quality evidence or absence of evidence associated with a number of the recommendations. The American Gastroenterological Association (AGA) would like to encourage future research to address these evidentiary limitations. Accordingly, the AGA will continue to monitor and assess new and potentially relevant evidence to determine whether updating of these recommendations is justified.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Yang YX, Brill J, Krishnan P, Leontiadis G, Clinical Guidelines Committee. American Gastroenterological Association Institute guideline onÂ the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology. 2015 Oct;149(4):1082-7. [7 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Oct

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Practice Guideline Committee

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Financial Disclosures/Conflicts of Interest

The members were required to complete disclosure statement. These statements are maintained at the American Gastroenterological Association (AGA) Institute headquarters in Bethesda, Maryland and pertinent disclosures are published with the report.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Gastroenterology Journal Web site.

Availability of Companion Documents

The following are available:

- American Gastroenterological Association Institute technical review on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology. 2015 Oct;149(4):1088–1118. Available from the Gastroenterology Journal Web site.
- American Gastroenterological Association Institute guideline on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions: clinical decision support tool. Gastroenterology. 2015 Oct;149(4):1119. Available from the Gastroenterology Journal Web site.
- AGA process for developing guidelines. 2014 Dec. Available from the American Gastroenterological Association (AGA) Web site.
- The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Available from the Clinical Gastroenterology and Hepatology Web site.

The technical review also has an accompanying continuing medical education (CME) activity available from the Gastroenterology Journal Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 2, 2016. The information was verified by the guideline developer on February 29, 2016.

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